DEPARTMENT OF HEALTH & HUMAN SERVICES
FDA, Center for Biologics Evaluation and Research

MEMORANDUM

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Subject: Product Review Memo for BLA Supplement 125260/0; DTaP-IPV, review of DT product issues

Sponsor: GlaxoSmithKline (GSK)

To: Joe Temenak, Ph.D., RPM; DVRPA, HFM-481, and file.

Summary/background:

On April 6, 2007 GSK submitted a Biologics License Application for Diphtheria and Tetanus Toxoids, Acellular Pertussis Vaccine Adsorbed and Inactivated Poliovirus Vaccine Combined (DTaP-IPV): the proposed proprietary name is Kinrix. The vaccine was investigated under IND [redacted] The vaccine is composed of the identical DTaP components in GSK's Infanrix vaccine with the addition of inactivated poliovirus vaccine (IPV). These components are also present in GSK's Pediarix vaccine at the same concentrations and are manufactured in an identical manner to the components in the currently licensed preservative-free Pediarix. DTaP-IPV is intended for immunization of children 4-6 years of age as a 5th dose of DTaP and 4th dose of IPV. The focus of this review is on the production and testing of the diphtheria and tetanus toxoid components in the candidate DTaP-IPV vaccine.

Supplement Review:

Diphtheria and Tetanus Toxoid Manufacture:

Production of the diphtheria and tetanus toxoids is performed by Novartis Vaccines and Diagnostics in Marburg Germany through a shared manufacturing arrangement with GSK. Novartis produces a DT concentrate for further manufacturing that is shipped to GSK and is used in several vaccines for the US market, including Infanrix, Pediarix, Boostrix and the candidate vaccine DTaP-IPV (Kinrix). The DTaP-IPV vaccine contains

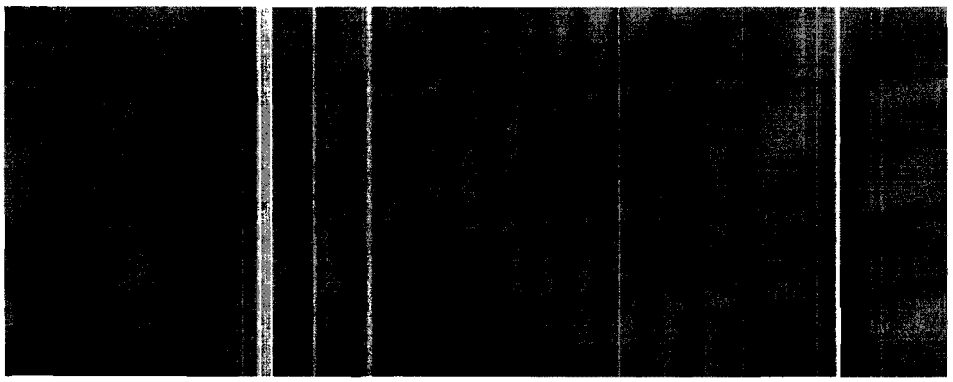
the following active ingredients shown in the Table below, which includes D and T components at 25 Lf and 10 Lf, respectively, and AlOH as the adjuvant as well as the excipients NaCl and WFI.

Composition of DTaP (Kinrix) Vaccine:

Active Ingredients	Quantity (per dose, 0.5 mL)
1. Pertussis toxin (PT)	25 µg
2. Filamentous haemagglutinin (FHA)	25 µg
3. Pertactin (69 kDa outer membrane protein – PRN)	8 µg
4. Diphtheria toxoid (D)	≥2 U/mL or 25 Lf
5. Tetanus toxoid (T)	≥2 U/mL or 10 Lf
6. Inactivated Poliovirus Type 1	40 DU
7. Inactivated Poliovirus Type 2	8 DU
8. Inactivated Poliovirus Type 3	32 DU
Adjuvant	
Aluminium hydroxide	[redacted]
Excipients	
NaCl	150 mM
Water for injection	q.s ad 0.5 mL

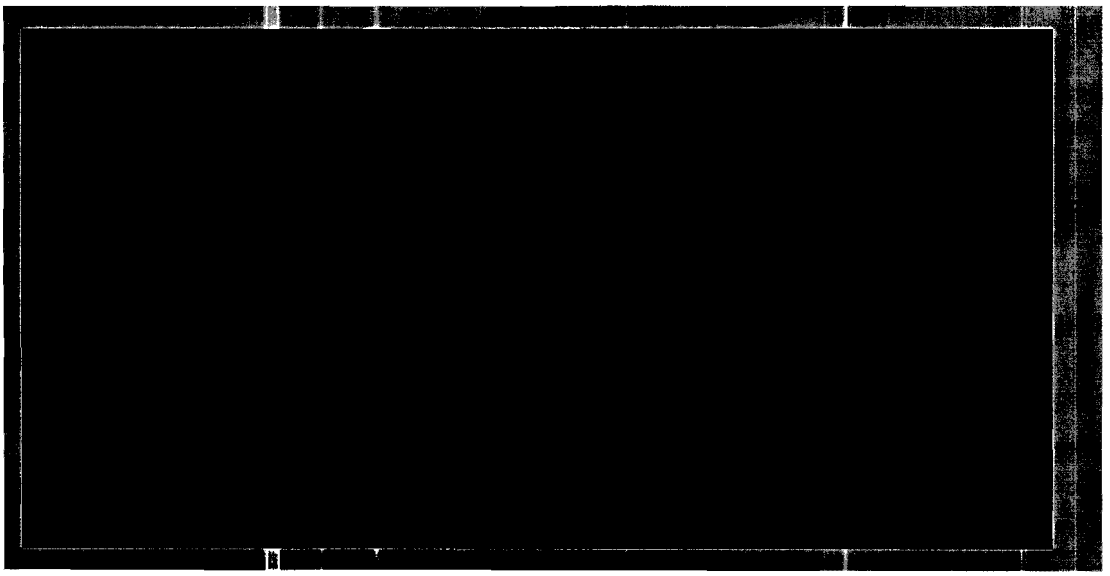
Although the DT adsorbed concentrate is tested for release at Novartis before shipment to GSK, the data for release was not provided in this submission. A telecon was held with GSK on June 13, 2007 in which release data and stability data for the DT concentrates was requested. GSK was able to provide Certificates of Analysis for the relevant DT lots but was not able to provide the additional requested information. GSK performs the test shown in the Table below upon receipt of shipments of DT concentrate from Novartis.

Test performed by GSK on DT concentrates:



Novartis Vaccines was approved in May 3, 2005 to manufacture a preservative-free DT concentrate at a scale of [redacted] and on January 17, 2007 was approved to manufacture the 2-PE free DT formulation at the [redacted] scale (STN 103648/5079).

The DT concentrate produced at Novartis contains the D and T components at a 2.5:1 ratio, which reflects the concentration of these components in the final formulated pediatric vaccines including DTaP-IPV (25 LF: 10 Lf). The method used to formulate Kinrix is shown below:



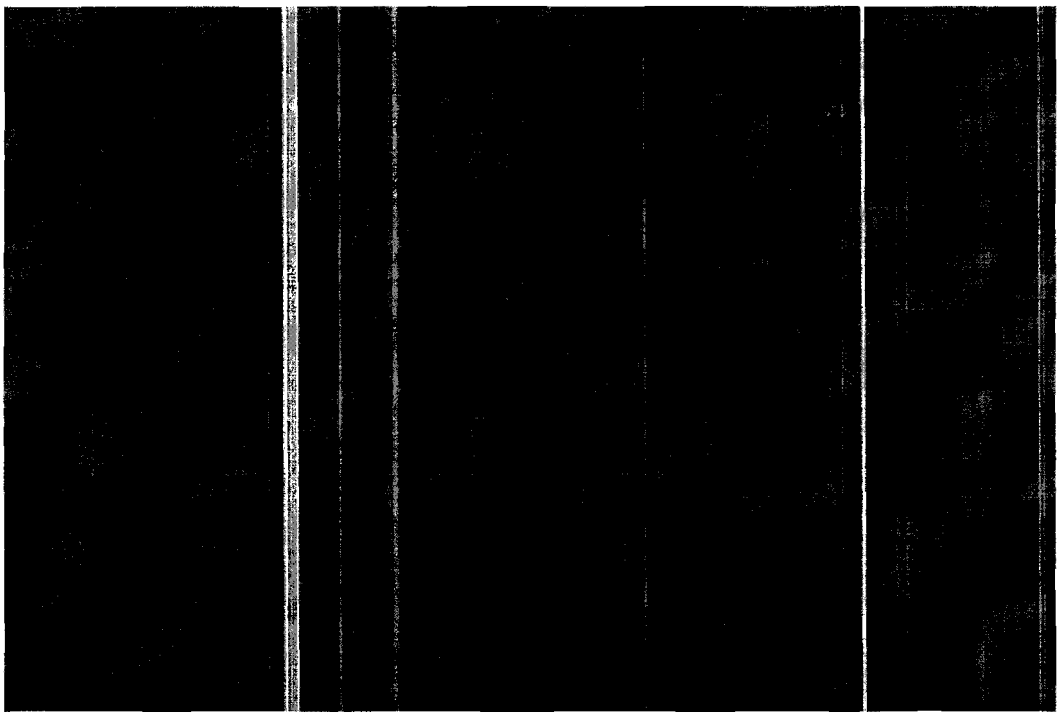
Manufacturing Development:

A series of manufacturing and formulation changes have occurred in the production of the candidate Kinrix vaccine since the IND was first submitted. Three series of lots have been produced, and the 1st and 2nd series lots were used in clinical studies 047/046 and 048 (pivotal study), respectively. The changes implemented for the 3rd series lots, which represent the current formulation, were used in the production of the commercial demonstration lots. The developmental changes are shown in the Table below:

Lot series	Lot N°	Manufacturing changes	Use
1st Series	20787A9	- aP with 2PE - DT with 2PE - IPV Type 1 and [redacted] working seeds - IPV Type [redacted] Master Seed - formulation with 2PE	- Study 213503/046 (PhII) - Study 213503/047 (PhII) - Stability
2nd Series	DC20A001A DC20A002A DC20A003A DC20A001B DC20A002B DC20A003B	**- aP without 2PE** **- DT without 2PE [redacted] scale)** **- IPV Type 1 and 3 Vero working seeds** **- IPV Type 2 Vero Master Seed** **- formulation without 2PE at pilot scale [redacted] tank)**	- Study 213503/048 (PhIII) - Stability
3rd Series	[redacted]	- aP without 2PE **- DT without 2PE [redacted] scale)** - IPV Type 1 and 3 Vero working seeds - IPV Type 2 Vero Master Seed **- formulation without 2PE at commercial scale [redacted] tank)**	- Representative of commercial formulation - Stability

Batch Analysis:

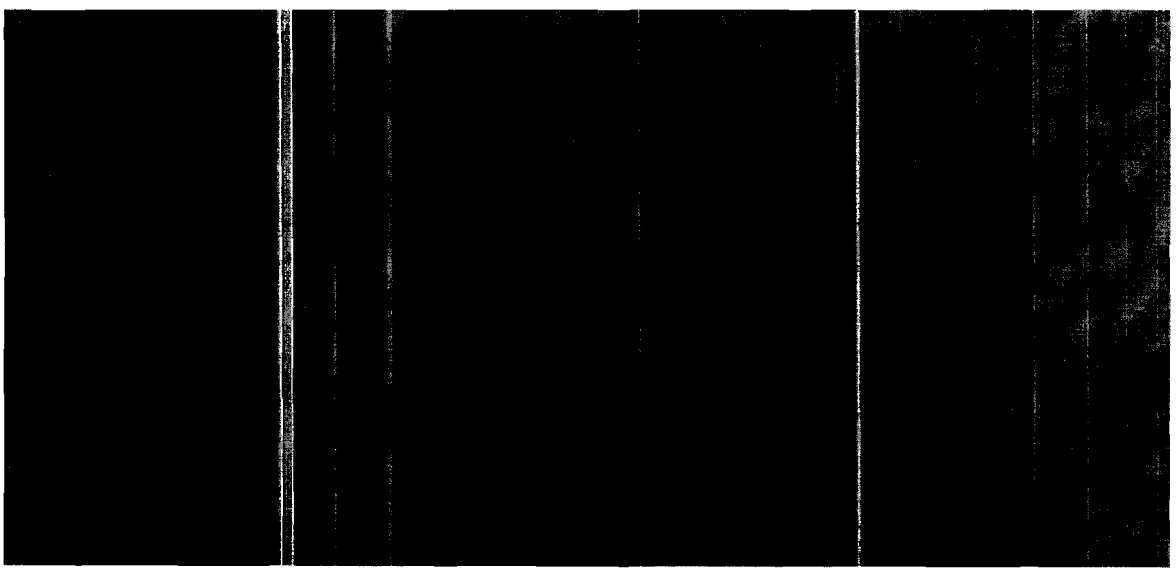
Information regarding production as well as release data and stability data for DT lots used in the production of the DTaP-IPV clinical consistency lots as well as the commercial demonstration lots were previously reviewed by myself and others in BLA supplements submitted by Novartis. DT concentrates used for production of the various DTaP lots are indicated below.



DT Lots 312010, 011, and 012 were used in the production of the clinical consistency lots and were produced at the [redacted] scale, while DT concentrate 312027 used for the commercial demonstration lots was produced at the [redacted] scale.

Release Test and Stability testing: No new tests for D and T toxoids have been introduced for this product. All tests used for the DTaP-IPV vaccine, both for release and stability, are currently done for the D and T components in Infanrix and Pediarix using the same specifications. The Tables below show the release test and specifications for final container and bulk for the candidate Kinrix vaccine:

Release Tests for Bulk:



Release Tests for Final Container:

Test	Method	Specification
1 Description	Visual inspection	Turbid liquid after shaking White deposit and colourless supernatant after sedimentation
2 Identity Diphtheria	[redacted]	[redacted]
3 Identity Tetanus		
4 Identity PT		
5 Identity FHA		
6 Identity PRN		
7 Identity Polio antigens		
8 pH		
9 Volume		
10 Aluminium content		
11 Sterility test FTM (30-35°C)	Membrane filtration (21 CFR 610 12)	Absence of growth
12 Sterility test TSB (20-25°C)	Membrane filtration (21 CFR 610 12)	Absence of growth
13 Endotoxin content	[redacted]	[redacted]
14 Potency IPV		
Type 1	ELISA	
Type 2	ELISA	
Type 3	ELISA	
15 General safety – Abnormal toxicity on guinea pigs	21 CFR 610 11	No weight loss, no abnormal reaction
16 General safety – Abnormal toxicity on mice	21 CFR 610 11	No weight loss, no abnormal reaction

Stability Testing:

Stability testing for the second series clinical consistency lots, which were made at pilot scale [redacted] have been completed through 36 months, the proposed expiry period for the product. Since the bulk is not held longer than [redacted] prior to filling, all stability testing is done on final containers. Additional data supporting the 36 month storage period for this product comes from stability studies for GSK's European licensed Kinrix vaccine, which contains the preservative 2-PE, but is otherwise identical to the US product. Potency data for D and T met all specifications through 36-months, and a 36-month expiry period is recommended for this product. The tables below list the stability protocol and the stability test used for the studies with the 2nd series clinical consistency lots:

Stability Testing Plan for the Clinical Consistency Lots:

Shelf-life target	:	**36 months**
Storage temperature	:	**+2°C to +8°C**
Testing frequency	:	**0 - 6 - 12 - 24 - 36 months**

Lot n°	Time 0	Time 6m*	Time 12m*	Time 18m*	Time 24m	Time 36m
DC20A001B	F	P	P	P	F	F
DC20A002B	F	P	P	P	F	F
DC20A003B	F	P	P	P	F	F

F = Full testing
P = Partial testing

[redacted]

Stability tests performed on the Clinical Consistency Lots:

Tests	Methods
[redacted]	[redacted]

Stability studies have also been initiated on four commercial demonstration lots [redacted] made at full scale using the same equipment that will be used for routine blending and formulation. Stability data through 9-months has been submitted for three of these lots. All tests including D and T potency have met specification at all time points. The stability protocol and test used for the stability study are shown in the Tables below:

Stability Protocol for Commercial Demonstration Lots:

Shelf-life target	**:**	**36 months**				
Storage temperature	**:**	**+2°C to +8°C**				
Testing frequency	**:**	**0 - 6 - 12 - 18 - 24 - 36 months**				
Lot n°	Time 0	Time 6m	Time 12m	Time 18m	Time 24m	Time 36m
[redacted]	F	P	S	P	F	F
	F	P	S	P	F	F
	F	P	S	P	F	F
	F	P	S	P	F	F

* syringe presentation, ** vial presentation
F = Full testing, S = Stability testing, P = Partial stability testing

Stability Tests for Commercial Demonstration Lots:

Tests	Methods
[redacted]	[redacted]

Comments/Recommendation

I have no concerns regarding the manufacture or testing of the diphtheria and tetanus toxoid components in the candidate Kinrix vaccine. Based on the stability studies done for the clinical consistency lots as well as supporting data from the Kinrix vaccine licensed outside the US, I recommend a 36-month expiry period for this product when stored at 2-8° C.